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METHODS AND COMPOSITIONS FOR TREATING DEPRESSION AND OTHER DISORDERS USING OPTICALLY PURE (-) SIBUTRAMINE

1. BACKGROUND OF THE INVENTION

This invention relates to novel compositions of matter containing optically pure (-) sibutramine. These compositions possess potent activity in treating depression. These compositions also possess potent activity in treating depression while avoiding the adverse effects, including but not limited to, significant increases in heart rate, increased blood pressure, psychomotor activity, dry mouth, and nervousness which are associated with the administration of the racemic mixture of sibutramine. The novel compositions of the present invention avoid said adverse effects while exhibiting a more rapid onset of action than that exhibited by racemic sibutramine. Additionally, these novel compositions of matter containing optically pure (-) sibutramine are useful in treating obesity or weight gain in a human. These compositions also possess potent activity in treating obesity and weight gain while avoiding the adverse effects which are associated with the administration of the racemic mixture of sibutramine.

In addition, these novel compositions of matter containing (-) sibutramine are useful in treating disorders ameliorated by inhibition of neuronal monoamine reuptake, because (-) sibutramine acts as a neuronal monoamine reuptake inhibitor. Several monoamines, the reuptake of which are inhibited by sibutramine include, but are not limited to, dopamine, noradrenaline (also known as norepinephrine), and serotonin. (King *et al. J. Clin*

Pharmac. 26: 607-611, 1989; Rees, United States Patent No. 4,871,774). Disorders ameliorated by neuronal monoamine reuptake inhibition include, but are not limited to, Parkinson's disease and depression. The novel compositions of the present invention also possess potent activity in treating disorders ameliorated by neuronal monoamine reuptake inhibition while avoiding the adverse effects associated with the administration of racemic sibutramine.

Furthermore, these novel compositions of matter containing optically pure or substantially optically pure (-) sibutramine are useful in treating cerebral function disorders. Such disorders include, but are not limited to, senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome and schizophrenia. Cerebral function disorders may be induced by factors including, but not limited to, cerebrovascular diseases such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries and the like and where symptoms include disturbances of consciousness, senile dementia, coma, lowering of attention, speech disorders and the like. The novel compositions of the present invention also possess potent activity in treating cerebral function disorders while avoiding the adverse effects associated with the administration of racemic sibutramine.

Further, the present invention encompasses methods for treating all of the above-described conditions in a human by administering optically pure or substantially optically pure (-) sibutramine to a human in need of such treatment. In addition, the

present invention encompasses methods for treating the above-described conditions in a human while avoiding the adverse effects associated with the racemic mixture of sibutramine.

1.1 Steric Relationships and Drug Action

Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes (-) and (+) or d and l are employed to designate the sign of rotation of plane-polarized light by the compound. A compound prefixed with (-) or l is levorotatory and a compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. Such a stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric or racemic mixture.

Stereochemical purity is of importance in the field of pharmaceuticals, where 12 of the 20 most prescribed drugs exhibit chirality. A case in point is provided by the L-form of the β-adrenergic blocking agent, propranolol, which is known to be 100 times more potent than the D-enantiomer.

Furthermore, optical purity is important since certain isomers may actually be deleterious and not simply inert. For example, the D-enantiomer of thalidomide is a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, while the corresponding L-enantiomer has been thought to be a potent teratogen.

The active compound of the present compositions and methods is an optical isomer of the compound sibutramine, which is described in United States Patent Nos. 4,746,680 and 4,522,828. Chemically, this optical isomer is (-) [N-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-N,N-dimethylamine. This isomer will hereinafter be referred to as (-) sibutramine which includes optically pure and substantially optically pure (-) sibutramine.

Sibutramine, the subject of the present invention, is available only as a racemic mixture. Sibutramine is generally administered as a hydrochloride salt, and frequently as the monohydrate.

The racemic mixture of sibutramine is used primarily in the treatment of depression which, along with mania, falls under the heading of affective disorders. Sibutramine is a monoamine reuptake inhibitor with activity against noradrenaline (also known as norepinephrine) and, to a lesser degree, against serotonin and dopamine (see Buckett, W.R. *et al., Prog. Neuro-Psychopharm. & Biol. Psychiat.* 12, 575-584, 1988; King, D.J. *et al., Brit. J. Clin. Pharmac.* 26, 607-611, 1988). Sibutramine is distinguished from other antidepressants by its profile of monoamine reuptake inhibition, rapid and potent down-regulation of cerebral-adrenergic mechanisms, a relative lack of anticholinergic side effects as compared to certain other classes of antidepressant agents, and a lack of activity as a monoamine oxidase inhibitor.

Mania, as well as depression, is characterized by changes in mood as the primary symptom. Either of these two extremes of mood may be accompanied by psychosis with disordered thought and

delusional perceptions. Psychosis may have, as a secondary symptom, a change in mood, and it is this overlap with depression that causes much confusion in diagnosis. Severe mood changes without psychosis frequently occur in depression and are often accompanied by anxiety.

Affective disorders, including major depression and bipolar manic-depressive illness, are characterized primarily by changes in mood. Major depression is the most common of the significant mental illnesses; it must be distinguished clinically from periods of normal grief, sadness, disappointment, and the related dysphoria or demoralization frequently associated with medical illness. Depression is characterized by feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, and self-deprecation. Physical changes can also occur, including insomnia, anorexia, weight loss, decreased energy, loss of libido, and disruption of hormonal circadian rhythms. Often the condition responds to tricyclic or related anti-depressant drugs, monoamine oxidase inhibitors, or in resistant cases or severe disease, to electro-convulsive shock treatment. The use of racemic sibutramine for the treatment of depression has been described in United States Patent No. 4,522,828.

Sibutramine may also be useful in treating dementia. Dementia, which includes Alzheimer's-type dementia, is produced by a degenerative process involving a loss of cerebral cortical cells; memory loss is a prominent symptom. Dementia is a syndrome of progressive and irreversible dysfunction, presumably caused by cerebral neuropathologic changes and cell loss. The condition is considered to be dominated by cognitive difficulties; depression,

paranoia, anxiety, and other psychologic symptoms may also be predominant. In sum, the common clinical profile is one of slow disintegration of both personality and intellect caused by impaired insight and judgment and by the loss of affect. Dementia is usually insidious, slowly progressive, and usually untreatable. However, in depressed, demented individuals, some antidepressants can significantly improve total function.

Alzheimer's type dementia may also be treated by antidepressant therapy. Alzheimer's type dementia (ATD) is a particularly devastating type dementia which affects 30% of humans over 80 years of age (see Evans *et al.*, *J.A.M.A.* 262: 2551-2556, 1989). ATD is a neurodegenerative disease characterized by gradual cognitive impairment. The etiology and pathogenesis of this dementia is associated histopathologically with amyloid plaques, neurofibrillary tangles and loss of neuronal mass primarily in the brain's temporal lobe and neocortex. All of the above mentioned conditions may occur as a result of cerebral function disorders or cerebrovascular disease, and as such, racemic sibutramine may provide treatment and relief from ATD.

Racemic sibutramine has also been used in the treatment of cerebral function disorders as described in United States Patent No. 4,939,175. Cerebral function disorders have a complex etiology; among their causes are cerebrovascular diseases such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, and head injuries and the like. Cerebral function disorders produce a variety of symptoms as secondary diseases, for example, disturbances of consciousness, coma, lowering of attention, amnestic syndrome, senile

dementia, speech disorder and the like. Racemic sibutramine has beneficial effects in the treatment of these symptoms based on its activation of the central nervous system through elevation of monoamine neurotransmitter levels at the presynaptic junction. It has also been found, as stated in U.S. Patent No. 4,937,175, that racemic sibutramine is especially useful for improving cerebral function in the treatment of symptoms which relate to intellectual deficits such as senile dementia, amnesia/amnestic syndrome, Parkinson's disease, Alzheimer's type dementia, memory loss, disturbance of consciousness, Lennox syndrome, autism, hyperkinetic syndrome and schizophrenia based on the increase of spontaneous movement and the enhancement of dopamine activity that sibutramine provides. However, there is a need for a drug having a high activity for treating the symptoms of these cerebral function disorders while excluding or reducing the adverse effects (side effects) associated with its use.

Furthermore, racemic sibutramine may be useful in treating weight disorders including obesity and weight gain. Obesity is characterized by an accumulation of body fat, to the extent that body weight is 20 percent greater than standard. The importance of the condition is in the number of medical complications to which obese individuals are subject. While the etiology of obesity is simple and relates to consuming more calories than are expended, many factors contribute to the condition.

The prognosis for obesity is poor; it is a chronic condition that is resistant to treatment and prone to relapse. Caloric reduction through diet, increased physical activity, radical surgical treatment, and medication are considered treatments

that may be employed in individual cases. Drug treatment of obesity is often governed by restrictive governmental regulation, and weight gain following this treatment modality is often greater than with other treatments. There is considerable opportunity for the development of safe and effective drug treatments. The use of racemic sibutramine for the treatment of obesity has been described in International Patent Publication Number WO 90/06110, published June 14, 1990, by Scheinbaum, J.L.

As discussed above, sibutramine is known to be an inhibitor of neuronal monoamine reuptake. Several monoamines, the reuptake of which are inhibited by sibutramine, include dopamine, noradrenaline (norepinephrine), and serotonin. One condition which has been linked to abnormal monoamine (dopamine) levels and which can be treated by neuronal monamine (dopamine) reuptake inhibition is Parkinson's disease, which is caused by degenerative changes in the ganglia at the base of the cerebrum. The use of racemic sibutramine to treat Parkinson's disease has been described in United States Patent Nos. 4,816,488 and 4,871,774.

Parkinson's disease, independent of a specific etiology, is a chronic, progressive central nervous system disorder that usually appears insidiously in the later decades of life. The disease produces a slowly increasing disability in purposeful movement. It is characterized by the major clinical features of tremor, bradykinesia, rigidity, and a disturbance of posture. Patients often have an accompanying dementia. In idiopathic parkinsonism, there is usually a loss of cells in the substantia nigra, locus ceruleus, and other pigmented neurons of the brain, and a decrease of dopamine content in nerve

axon terminals of cells projecting from the substantia nigra. The understanding that Parkinson's disease is a syndrome of dopamine deficiency resulted from a series of basic and clinical observations.

While the racemic mixture of sibutramine has the foregoing advantages, it also has disadvantages such as causing adverse effects, including, but not limited to, significant increases in supine and standing heart rate, increased blood pressure, increased psychomotor activity, dry mouth, tension and nervousness. These cardiovascular effects and psychostimulant properties may significantly limit the dose level, frequency, and duration of drug therapy. Moreover, while racemic sibutramine is faster acting than other classes of antidepressants, even more rapid onset of action would be desirable. Thus, it would be desirable to find a compound with the advantages of racemic sibutramine which would not have the aforementioned disadvantages.

2. SUMMARY OF THE INVENTION

This invention relates to novel compositions of matter containing optically pure (-) sibutramine. The compositions possess potent activity as antidepressants. These compositions also possess potent activity as antidepressants while avoiding adverse effects including but not limited to significant increases in heart rate, increased blood pressure, psychomotor activity, dry mouth, and nervousness which are associated with the administration of the racemic mixture of sibutramine. Additionally, optically pure or substantially optically pure (-) sibutramine exhibits more rapid onset of action in this respect than does the racemic form of the drug. Further, the novel compositions of

matter of the present invention containing (-) sibutramine are useful in treating obesity and weight gain in a human. These compositions also possess potent activity in treating obesity and weight gain in a human while avoiding the adverse effects which are associated with the administration of the racemic mixture of sibutramine.

Also disclosed are novel compositions of matter containing (-) sibutramine which possess potent activity in treating disorders ameliorated by inhibition of neuronal monoamine reuptake. These compositions also possess potent activity in treating such disorders (e.g., Parkinson's disease) while avoiding the adverse effects which are associated with the racemic mixture of sibutramine.

In addition, novel compositions of matter containing (-) sibutramine are useful in treating cerebral function disorders. These composition possess potent activity in treating cerebral function disorders while avoiding the adverse effects associated with the administration of the racemic mixture of sibutramine.

Further, the present invention discloses methods for treating the above-described conditions in a human by administering optically pure or substantially optically pure (-) sibutramine. The present invention also discloses methods for treating the above-described conditions in a human by administering optically pure or substantially optically pure (-) sibutramine while avoiding the adverse effects associated with the racemic mixture of sibutramine.

3. DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of treating depression in a human which comprises administering to a human in need of antidepressant therapy, an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate the human's depression.

The present invention further encompasses a method of treating depression in a human which comprises administering to a human in need of antidepressant therapy, an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate the human's depression but insufficient to cause adverse effects associated with racemic sibutramine. (-) Sibutramine can treat depression while exhibiting a more rapid onset of action than racemic sibutramine.

The present invention also encompasses an antidepressant composition for the treatment of a human in need of antidepressant therapy which comprises an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate depression.

The present invention also encompasses an antidepressant composition for the treatment of a human in need of antidepressant therapy which comprises an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate depression but insufficient to cause adverse effects associated with

racemic sibutramine. These novel compositions avoid adverse effects while exhibiting a more rapid onset of action than that of racemic sibutramine.

Further, the present invention encompasses a method of treating obesity or weight gain in a human, which comprises administering to a human in need of a reduction in weight, an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to bring about a weight reduction in said human.

Further, the present invention encompasses a method of treating obesity or weight gain in a human, which comprises administering to a human in need of a reduction in weight, an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to bring about a weight reduction in said human, but insufficient to cause adverse effects associated with administration of racemic sibutramine.

The present invention also encompasses a composition for treating obesity or weight gain, which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to achieve weight loss.

In addition, the present invention encompasses a composition for treating obesity or weight gain, which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to achieve weight loss but insufficient to cause the adverse effects of racemic sibutramine.

The present invention also encompasses a method of treating disorders ameliorated by neuronal monoamine reuptake inhibition in a human which comprises administering to a human in need of neuronal monoamine reuptake inhibition, an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to treat such disorders. Disorders which are ameliorated by neuronal monoamine reuptake include, but are not limited to Parkinson's disease and depression.

The present invention further encompasses a method of treating disorders ameliorated by neuronal monoamine reuptake inhibition in a human which comprises administering to a human in need of neuronal monoamine reuptake inhibition, an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to treat said disorders but insufficient to cause the adverse effects associated with administration of racemic sibutramine.

Additionally, the present invention encompasses a composition for treating disorders ameliorated by neuronal monoamine reuptake inhibition in a human which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate said disorders.

The present invention encompasses a composition for treating disorders ameliorated by neuronal monoamine reuptake inhibition in a human which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said

amount being sufficient to alleviate said disorders but insufficient to cause adverse effects associated with racemic sibutramine.

The present invention also encompasses a method of treating cerebral function disorders which comprises administering to a human in need of treatment for a cerebral function disorder, an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate said cerebral function disorder.

The present invention also encompasses a method of treating cerebral function disorders which comprises administering to a human in need of treatment for a cerebral function disorder, an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate said cerebral function disorder, but insufficient to cause the adverse effects associated with administration of racemic sibutramine. Cerebral function disorders within the scope of the present invention include, but are not limited to, senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome and schizophrenia. Cerebral function disorders may be caused by cerebrovascular diseases such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries and the like.

In addition, the present invention encompasses a composition for treating cerebral function disorders which comprises an amount of (-)

sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to treat cerebral function disorders.

In addition, the present invention also encompasses a composition for treating cerebral function disorders which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to treat cerebral function disorders, but insufficient to cause adverse effects associated with racemic sibutramine.

The available racemic mixture of sibutramine (*i.e.*, a mixture of two enantiomers) exhibits antidepressant activity and provides therapy and/or a reduction of symptoms in a variety of conditions and disorders; however this racemic mixture, while offering the expectation of efficacy, causes adverse effects. Utilizing the optically pure or substantially optically pure (-) isomer of sibutramine results in clearer dose-related definitions of efficacy, diminished adverse effects, and accordingly an improved therapeutic index. It is, therefore, more desirable to use the (-) isomer of sibutramine than to use racemic sibutramine.

The term "adverse effects" as used herein includes, but is not limited to increases in heart rate, increases in blood pressure including systolic blood pressure, increased psychomotor activity, dry mouth, tension, and nervousness.

The term "substantially free of its (+) stereoisomer", as used herein, means that the composition contains a greater proportion of the (-) stereoisomer of sibutramine in relation to the (+) isomer of sibutramine. In a preferred embodiment of

the present invention the term "substantially free of its (+) stereoisomer" as used herein means that the composition contains at least 90% by weight of (-) sibutramine and 10% by weight or less of (+) sibutramine. In the most preferred embodiment, the term "substantially free of its (+) stereoisomer" means that the composition contains at least 99% by weight of (-) sibutramine and 1% or less of (+) sibutramine. In another preferred embodiment, the term "substantially free of its (+) stereoisomer" as used herein means that the composition contains 100% by weight of the (-) isomer of sibutramine. The above percentages are based on the total amount of sibutramine present in the composition. The terms "substantially optically pure (-) sibutramine", "optically pure (-) sibutramine" and "(-) isomer of sibutramine" are also encompassed by the above described amounts.

The term "a method of treating depression", as used herein, means relief from the symptoms of depression which include, but are not limited to, changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, and self-deprecation. Physical changes may also be relieved including insomnia, anorexia, weight loss, decreased energy and libido, and the return of normal hormonal circadian rhythms.

The term "a method for treating obesity or weight gain" as used herein, means reduction of weight, relief from being overweight, relief from gaining weight, or relief from obesity; all of which are usually due to extensive consumption of food.

The term "a method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake" as used herein, means relief from symptoms

of disease states associated with abnormal neuronal monoamine levels; such symptoms are reduced by way of neuronal monoamine reuptake inhibition. Monoamines, the reuptake of which are inhibited by the compositions and methods of the present invention, include, but are not limited to noradrenaline (or norepinephrine), serotonin and dopamine. One disorder treated by neuronal monoamine reuptake inhibition is Parkinson's disease.

The term "method of treating Parkinson's disease" as used herein means relief from the symptoms of Parkinson's disease which include, but are not limited to, slowly increasing disability in purposeful movement, tremors, bradykinesia, rigidity, and a disturbance of posture in humans.

The term "a method for treating cerebral function disorders" as used herein, means relief from the disease states associated with cerebral function disorders involving intellectual deficits which include but are not limited to, senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbances of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome and schizophrenia. Also within the meaning of cerebral function disorders are disorders caused by cerebrovascular diseases including, but not limited to, cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries and the like and where symptoms include disturbances of consciousness, senile dementia, coma lowering of attention, speech disorders and the like.

The optically purified stereoisomers of sibutramine are most readily obtained by resolving the

racemic mixture of sibutramine prepared by following synthetic procedures described in U.S. Patent Nos. 4,522,828 and 4,746,680, the disclosures of which are hereby incorporated by reference. The resolution of racemates by the fractional crystallization of diastereomeric salts formed with optically active resolving agents is a commonly used, conventional technique. See, for example, "Enantiomers, Racemates and Resolutions," by J. Jacques, A. Collet, and S.H. Wilen, (Wiley-Intenscience, New York, 1981); and S.H. Wilen, A. Collet, and J. Jacques, *Tetrahedron*, 33, 2725 (1977), "Stereochemistry of Carbon Compounds", by E.L. Eliel (McGraw-Hill, NY, 1962), and S.H. Wilen, p. 268, in "Tables of Resolving Agents and Optical Resolutions" (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

Since sibutramine is a basic amine, diastereomeric salts suitable for separation by fractional crystallization are readily formed by addition of chiral acid resolving agents in optically pure form. Suitable resolving agents for use herein include optically pure tartaric acid and its derivatives, camphorsulfonic acid, mandelic acid and derivatives thereof, and other optically active acids. The desired (-) sibutramine isomer may be recovered either from the crystallized diastereomer or from the mother liquor, depending on the solubility properties of the particular acid resolving agent employed and depending on the particular acid enantiomer used. The identity and optical purity of the particular sibutramine isomer so recovered may be determined by polarimetry or other analytical methods.

The magnitude of a prophylactic or therapeutic dose of (-) sibutramine in the acute or chronic management of disease will vary with the

severity of the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to age, body weight, response, and the past medical history of the individual patient. In general, the recommended daily dose range for the conditions described herein lie within the range of from about 1 mg to about 60 mg per day, given as a single once-a-day dose in the morning or as divided doses throughout the day. Preferably, a daily dose range should be from about 2 mg to about 50 mg per day; and most preferably, a daily dose range should be between about 5 mg and about 45 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 5 to about 15 mg, and increased if necessary up to about 45 mg per day as either a single dose or divided doses, depending on the patient's global response. It is further recommended that patients aged over 65 years should receive doses in the range of about 5 to about 30 mg per day depending on global response. It may be necessary to use dosages outside these ranges.

The various terms "said amount being sufficient to alleviate depression", "said amount being sufficient to alleviate Parkinson's disease", "said amount being sufficient to alleviate obesity or weight gain", "an amount sufficient to achieve weight loss", "said amount being sufficient to bring about weight reduction in said human", "said amount being sufficient to alleviate dementia", "said amount sufficient to alleviate said disorders ameliorated by inhibition of neuronal monoamine reuptake", "said amount is sufficient to alleviate cerebral function disorders" wherein said disorders are selected from the group consisting of senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome,

disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome, schizophrenia, and cerebrovascular diseases such as cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries and the like, are encompassed by the above described dosage amounts and dose frequency schedule.

The various terms "said amount being sufficient to alleviate depression but insufficient to cause said adverse effects of racemic sibutramine", "said amount being sufficient to alleviate Parkinson's disease but insufficient to cause said adverse effects of racemic sibutramine", "said amount being sufficient to alleviate obesity or weight gain but insufficient to cause said adverse effects of racemic sibutramine", "an amount sufficient to achieve weight loss but insufficient to cause said adverse effects of racemic sibutramine", "said amount being sufficient to bring about weight reduction in said human but insufficient to cause said adverse effects of racemic sibutramine", "said amount being sufficient to alleviate dementia but insufficient to cause said adverse effects of racemic sibutramine", "said amount sufficient to alleviate said disorders ameliorated by inhibition of neuronal monoamine reuptake but insufficient to cause said adverse effects of racemic sibutramine", "said amount is sufficient to alleviate cerebral function disorders wherein said disorders are selected from the group consisting of senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, disturbance of consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autism, hyperkinetic syndrome, schizophrenia, and cerebrovascular diseases such as

cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries and the like but insufficient to cause said adverse effects of racemic sibutramine" are encompassed by the above described dosage amounts and dose frequency schedule.

Any suitable route of administration may be employed for providing the patient with an effective dosage of (-) sibutramine. For example, oral, rectal, parenteral (intravenous, intramuscular), transdermal, subcutaneous, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise (-) sibutramine as active ingredient or a pharmaceutically acceptable salt thereof and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients known to those skilled in the art. The term, "pharmaceutically acceptable salts", refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

Since the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic,

phosphoric, and sulfuric acids, and most particularly preferred is the hydrochloride salt.

The compositions include compositions suitable for oral, rectal, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The most preferred route of administration of the present invention is the oral route. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the part of pharmacy.

In the case where an oral composition is employed, a suitable dosage range for use is, *e.g.* from about 1 mg to about 60 mg per day, generally given as a single once-a-day dose in the morning. The preferable dose range will be from about 2 to about 50 mg per day, generally given once a day, and most preferably from between about 5 mg and about 45 mg per day. As aforementioned, the patient should be upwardly titrated from below to within this dosage range to satisfactorily control symptoms.

In practical use, (-) sibutramine can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (e.g., intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and

elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used in the case of oral solid preparations such as, for example, powders, capsules, and tablets, with the solid oral preparations being preferred over the liquid preparations. The most preferred solid oral preparation is tablets.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and/or delivery devices such as those described in United States Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200; 4,008,719; 4,687,660; and 4,769,027, the disclosures of which are hereby incorporated by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosol sprays each containing a predetermined amount of the active ingredient as a powder or granules, a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more necessary

ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Desirably, each tablet contains from about 1 mg to about 60 mg of the active ingredient and each cachet or capsule contains from about 1 mg to about 60 mg of the active ingredient. Most preferably, the tablet, cachet, or capsule contains either one of three dosages, *e.g.*, about 10 mg, about 20 mg, or about 30 mg of active ingredient (as scored tablets, the preferable dose form).

The invention is further defined by reference to the following examples describing in detail, the preparation of the compositions of the present invention.

It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

All temperatures are in degrees Celsius.

4. EXAMPLES

4.1. Example 1 PHARMACOLOGICAL STUDY TO DETERMINE THE RELATIVE POTENCY AND PROFILE OF SPECIFICITY OF OPTICALLY PURE AND RACEMIC SIBUTRAMINE AS INHIBITORS OF MONOAMINE REUPTAKE

A pharmacologic study is conducted to determine the relative potency, comparative efficacy, binding affinity, and toxicity of the enantiomers and racemic mixture of sibutramine. The profile of relative specificity of monoamine reuptake inhibition is determined from the compound's inhibition of norepinephrine (NE) (variously known as noradrenaline) reuptake in brain tissue with that of the inhibition of dopamine (DA) and serotonin (5HT) reuptake.

High-affinity uptake of the ^{3}H-radiomonoamines is studied in synaptosomal preparations prepared from rat corpus striatum (for inhibition of DA reuptake) and cerebral cortex (for 5HT and NE) using methods published by Kula *et al.*, *Life Sciences* 34(26): 2567-2575, 1984, and Baldessarini *et al.*, *Life Sciences* 39: 1765-1777, 1986. Tissues are freshly dissected on ice and weighed. Following homogenization by hand (14 strokes in 10-35 vols of ice-cold isotonic 0.32M sucrose, containing nilamide, 34 μM) in a Teflon-on-glass homogenizer, the tissue is centrifuged for ten (10) minutes at 900 x g; the supernatant 'solution' that results contains synaptosomes that are used without further treatment. Each assay tube contains 50 μL of the cerebral homogenate, radiolabelled-^{3}H-monoamine, and the test compound (*e.g.*, the pure sibutramine enantiomers, the racemate, and appropriate standards) in a freshly prepared physiologic buffer solution with a final volume of 0.5 mL. Tissues are preincubated for 15 minutes at 37°C before the assay. Tubes are held on ice until the start of incubation which is

initiated by adding ^{3}H-amine to provide a final concentration of 0.1 μM. Tubes are incubated at 37°C for 10 minutes with ^{3}H-DA (26 Ci/mmol) and for 20 minutes with ^{3}H-5HT (about 20 Ci/mmol) and ^{3}H-NE (about 10 Ci/mmol). The specific activity of the radiomonoamine will vary with available material and is not critical. The reaction is terminated by immersion in ice and dilution with 3 ml of ice cold isotonic saline solution containing 20 mM TRIS buffer (pH 7.0). These solutions are filtered through cellulose ester microfilters, followed by washing with two 3 mL volumes of the same buffer. The filter is then counted for ^{3}H-radioactivity in 3.5 mL of Polyfluor at ~ 50% efficiency for tritium. Blanks (either incubated at 0°C or incubated with specific, known uptake inhibitors of DA [GRB-12909, 10 μM], 5HT [zimelidine 10 μM], or of NE [desipramine 10 μM]) are usually indistinguishable from assays performed without tissue and average 2-3% of total CPM.

Comparison of the amounts of ^{3}H-radioactivity retained on the filters provides an indication of the relative abilities of the pure enantiomers and racemic mixture of sibutramine (and of known DA-, 5HT-, or NE-reuptake inhibitors) to block the reuptake of these monoamines in those tissues. This information is useful in gauging the relative potency and efficacy of racemic sibutramine and its enantiomers.

The acute toxicities of the enantiomers of sibutramine and of the racemic mixture thereof are determined in studies in which rats are administered progressively higher doses (mg/kg) of the pure isomers or racemate. That lethal dose which, when administered orally, causes death of 50% of the test animals, is reported as the LD_{50}. Comparison of LD_{50}

values for the enantiomers and racemate provides a measure of the relative toxicity of the compositions.

4.2. Example 2

ORAL FORMULATION

Capsules:

Formula	Quantity per Capsule in mg		
Active ingredient (-) sibutramine	A 10.0	B 20.0	C 30.0
Lactose	70.0	60.0	95.0
Corn Starch	19.5	19.5	24.5
Magnesium Stearate	0.5	0.5	0.5
Compression Weight	100.0	100.0	150.0

The active ingredient, (-) sibutramine, the lactose and corn starch are blended until uniform; then the magnesium stearate is blended into the resulting powder. The resulting mixture is encapsulated into suitably sized two-piece hard gelatin capsules.

4.3. Example 3

ORAL FORMULATION

Tablets:

Formula	Quantity per Tablet in mg		
Active ingredient	A	B	C
(-) sibutramine	10	20	30
Lactose	94	84	74
Starch BP	30	30	30
Pregelatinized Maize Starch	15	15	15
Magnesium Stearate	1	1	1
Compression Weight	150	150	150

The active ingredient is sieved through a suitable sieve and blended with lactose, starch, and pregelatinized maize starch. Suitable volumes of purified water are added, and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using punches.

Tables of other strengths may be prepared by altering the ratio of active ingredient to lactose or to the compression weight and using punches to suit.

What is claimed is:

1. A method of treating depression in a human which comprises administering to a human in need of antidepressant therapy, an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate depression.

2. A method of treating depression in a human according to claim 1 in which said amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, is sufficient to alleviate depression but insufficient to cause adverse effects associated with the administration of racemic sibutramine.

3. The method of claims 1 or 2 wherein (-) sibutramine is administered by intravenous infusion, transdermal delivery, or orally as a tablet or a capsule.

4. The method of claim 3 wherein the amount administered is from about 1 mg to about 60 mg per day.

5. The method of claim 4 wherein the amount administered is from about 2 mg to about 50 mg per day.

6. The method of claim 5 wherein the amount administered is from about 5 mg to about 45 mg per day.

7. The method of claim 3 wherein the amount of (-) sibutramine or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of sibutramine.

8. The method of claim 3 wherein the (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer,

is administered together with a pharmaceutically acceptable carrier.

9. The method according to claim 3 wherein (-) sibutramine is administered as a hydrochloride salt.

10. A composition for the treatment of depression in a human which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate depression.

11. A composition for the treatment of depression in a human according to claim 10 wherein said amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, is sufficient to treat depression but insufficient to cause adverse effects associated with the administration of racemic sibutramine.

12. A composition according to claim 10 or 11 wherein said amount is from about 1 mg to about 60 mg.

13. A composition according to claims 10 or 11 wherein (-) sibutramine is in the form of a hydrochloride salt.

14. A composition according to claim 12 wherein said composition is adapted for oral administration.

15. A composition according to claim 12 adapted for intravenous delivery.

16. A composition according to claim 12 adapted for use in a transdermal patch.

17. The composition according to claim 12 which comprises (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, and a pharmaceutically acceptable carrier.

18. A method for treating obesity or weight gain in a human which comprises administering to a human in need of a reduction in weight, an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate obesity or weight gain.

19. A method for treating obesity or weight gain in a human according to claim 18 wherein said amount is sufficient to alleviate obesity or weight gain but insufficient to cause the adverse effects associated with administration of racemic sibutramine.

20. The method of claims 18 or 19 wherein (-) sibutramine is administered by intravenous infusion, transdermal delivery, or orally as a tablet or a capsule.

21. The method of claim 20 wherein the amount administered is from about 1 mg to about 60 mg per day.

22. The method of claim 21 wherein the amount administered is from about 2 mg to about 50 mg per day.

23. The method of claim 22 wherein the amount administered is from about 5 mg to about 45 mg per day.

24. The method of claim 23 wherein the amount of (-) sibutramine or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of sibutramine.

25. The method of claim 20 wherein the (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, is administered together with a pharmaceutically acceptable carrier.

26. The method according to claims 18 or 19 wherein (-) sibutramine is administered as a hydrochloride salt.

27. A composition for treating obesity or weight gain in a human which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate obesity or weight gain.

28. A composition for treating weight disorders in a human according to claim 27 wherein said amount is sufficient to alleviate obesity or weight gain in a human but insufficient to cause adverse effects associated with administration of racemic sibutramine.

29. A composition according to claims 27 or 28 wherein the amount is about 1 mg to about 60 mg.

30. A composition according to claim 27 or 28 wherein (-) sibutramine is in the form of a hydrochloride salt.

31. A composition according to claim 29 wherein said composition is adapted for oral administration.

32. A composition according to claim 29 adapted for intravenous delivery.

33. A composition according to claim 29 adapted for use in a transdermal patch.

34. The composition according to claim 29 which comprises (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, and a pharmaceutically acceptable carrier.

35. A method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake in a human which comprises administering to a

human in need of such treatment an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate said disorders.

36. A method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake in a human according to claim 35 in which said amount is sufficient to alleviate said disorders but insufficient to cause adverse effects associated with administration of racemic sibutramine.

37. A method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake in a human according to claims 35 or 36 wherein said monoamine is dopamine.

38. A method of treating disorders ameliorated by inhibition of neuronal monoamine reuptake in a human according to claims 35 or 36 wherein said disorder is Parkinson's disease.

39. The method of claims 35 or 36 wherein (-) sibutramine is administered by intravenous infusion, transdermal delivery, or orally as a tablet or a capsule.

40. The method of claim 39 wherein the amount administered is from about 1 mg to about 60 mg per day.

41. The method of claim 40 wherein the amount administered is from about 2 mg to about 50 mg per day.

42. The method of claim 41 wherein the amount administered is from about 5 mg to about 45 mg per day.

43. The method of claim 39 wherein the amount of (-) sibutramine or a pharmaceutically

acceptable salt thereof is greater than approximately 90% by weight of the total amount of sibutramine.

44. The method of claim 39 wherein the (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer is administered together with a pharmaceutically acceptable carrier.

45. The method according to claim 39 wherein (-) sibutramine is administered as a hydrochloride salt.

46. A composition for the treatment of disorders ameliorated by inhibition of neuronal monoamine reuptake in a human which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate said disorders.

47. A composition for the treatment of disorders ameliorated by inhibition of neuronal monoamine reuptake in a human according to claim 46 wherein said amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, is sufficient to treat said disorders but insufficient to cause adverse effects associated with the administration of racemic sibutramine.

48. A composition according to claims 46 or 47 wherein the amount is about 1 mg to about 60 mg.

49. A composition according to claims 46 or 47 wherein (-) sibutramine is in the form of a hydrochloride salt.

50. A composition according to claim 48 wherein said composition is adapted for oral administration.

51. A composition according to claim 48 adapted for intravenous delivery.

52. A composition according to claim 48 adapted for use in a transdermal patch.

53. The composition according to claim 48 which comprises (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, and a pharmaceutically acceptable carrier.

54. A method for treating cerebral function disorders in humans which comprises administering to a human an amount of (-) sibutramine, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate cerebral function disorders.

55. A method for treating cerebral function disorders in a human according to claim 54 wherein said amount of (-) sibutramine or a pharmaceutically acceptable thereof, substantially free of its (+) stereoisomer, is sufficient to alleviate cerebral function disorders but insufficient to cause adverse effects associated with administration of racemic sibutramine.

56. A method for treating cerebral function disorders in a human according to claims 54 or 55 wherein said disorder is caused by a cerebrovascular disease.

57. A method for treating cerebral function disorders in a human according to claims 54 or 55 wherein said cerebral function disorder is selected from the group consisting of senile dementia, Alzheimer's type dementia, memory loss and amnesia/amnestic syndrome.

58. A method for treating cerebral function disorders in a human according to claim 56 wherein said cerebrovascular disease is selected from the

group consisting of cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis and head injuries.

59. The method of claims 54 or 55 wherein (-) sibutramine is administered by intravenous infusion, transdermal delivery, or orally as a tablet or a capsule.

60. The method of claim 59 wherein the amount administered is from about 1 mg to about 60 mg per day.

61. The method of claim 60 wherein the amount administered is from about 2 mg to about 50 mg per day.

62. The method of claim 61 wherein the amount administered is from about 5 mg to about 45 mg per day.

63. The method of claim 59 wherein the amount of (-) sibutramine or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total amount of sibutramine.

64. The method of claim 59 wherein the (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, is administered together with a pharmaceutically acceptable carrier.

65. The method according to claim 59 wherein (-) sibutramine is administered as a hydrochloride salt.

66. A composition for treating cerebral function disorders, which comprises an amount of (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate cerebral function disorders.

67. A composition for treating cerebral function disorders according to claim 66 wherein said amount of (-) sibutramine or a pharmaceutically salt thereof, substantially free of its (+) stereoisomer, is sufficient to treat cerebral function disorders but insufficient to cause the adverse effects associated with the administration of racemic sibutramine.

68. A composition according to claims 66 or 67 wherein the amount is about 1 mg to about 60 mg.

69. A composition according to claims 66 or 67 wherein (-) sibutramine is in the form of a hydrochloride salt.

70. A composition according to claim 68 wherein said composition is adapted for oral administration.

71. A composition according to claim 68 adapted for intravenous delivery.

72. A composition according to claim 68 adapted for use in a transdermal patch.

73. The composition according to claim 68 which comprises (-) sibutramine or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/05966

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 31/135
US CL : 514/646,650
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/646,650

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS, B10515- subutramine and its isomers for treatment of depression, obesity, Porkinson's disease, cerebral function disorders dementia and etcetera.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,522,828 (Jeffery et al.) 11 June 1985. See entire document.	1-73
Y	US, A, 4,746,680 (Jeffery et al.), 24 May 1988. See entire document.	1-73
Y	US, A, 4,806,570 (Jeffery et al.) 21 February 1989. See entire document	1-73
Y	US, A, 4,814,352 (Jeffery et al.) 21 March 1989. See entire document.	1-73
Y	US, A, 4,929,629 (Jeffery) 29 May 1990. See entire document	1-73

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/05966

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A,4,939,175 (Ukai et al) 03 July 1990. See entire document.	1-73
Y	PCT Publication No. WO/0611, The Boots Company PLC), 14 June 1990. See the abstract particulary.	1-73
Y	GB, A, 2098602 (The Boots Company PLC), 24 November 1982. See entire document	1-73
Y	EPA, A, 35597 (Rohm Pharma GMBH) 27 January 1982. See entire document	1-73
Y	US, A, 5,104,899 (Young et al.) 14 April 1992. See entire document	1-73